UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/517,074	04/19/2005	John Arthur Hohneker	ON/4-32515A	8731

1095 7590 07/24/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
07/24/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/517,074	HOHNEKER ET AL.	
	Examiner	Art Unit	
	BRANDON J. FETTEROLF	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-50* is/are pending in the application.

4a) Of the above claim(s) *43 and 46-49* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-42,44,45 and 50* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/01/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *STN Structure*.

DETAILED ACTION

Election/Restrictions

The Election filed on April 30, 2008 in response to the Restriction Requirement of April 2, 2008 has been entered. Applicant's election of Group I, claims 20-42, 44, 45 and 50, as specifically drawn to the special technical feature of a combination which comprises (a) a HER-1 or HER-2 antibody or (b) at least one anti-neoplastic agent and (c) an epothilone derivateive of formula I has been acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

The restriction requirement is therefore deemed to be proper and is made FINAL.

Claims 20-50 are pending.

Claims 43 and 46-49 are withdrawn from consideration as being drawn to non-elected inventions.

Claims 20-42, 44-45 and 50 are currently under examination.

Information Disclosure Statement

The information disclosure statement filed on 9/01/2005 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein which has been "lined through" has not been considered.

Specification

The use of a variety of trademark's such as Taxol® and Taxotere ® have been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 20, 22-23, 25, 27-28, 31-35, 37, 44-45 and 50 are rejected under 35 U.S.C. 102(b) as being anticipated by Vite et al. (WO 99/02514 A2, 1999).

Vite et al. teach a combination which comprises (a) a growth factor inhibitor such as a HER2 receptor monoclonal antibody or (b) a topoisomerase I or II inhibitor and (c) a epothilone derivative which appears to encompass the claimed epothilone derivaties of formula I (page 2, Compound V and page 10, lines 22-29). Moreover, the WO document teaches that the compounds can be formulated with a pharmaceutical vehicle or diluent (page 11, lines 4-6). Lastly, the WO document teaches that epothilones A and B have been found to exert microtubule-stabilizing effects similar to paclitaxel and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease (page 1, lines 9-20).

Claims 20, 22-23, 25-27, 32-38, 40-42, 44-45 and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Danishefsky et al. (US 2002/0058286 A1, IDS, filed 3/1/2001).

Danishefsky et al. teach a combination which comprises (a) at least one antineoplastic agent including, but not limited to, soundke oiusins syc as Paclitaxel, podophyllotoxins such as irinotecan, antibiotics such as doxorubicin and hormones such as tamoxifen (paragraph 0334). Moreover, the publication teaches that the combinations can be in the form or a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions (paragraph 0335).

Claims 20, 22-28, 30-42, 44-45 and 50 are rejected under 35 U.S.C. 102(e) as being anticipated by Lee et al. (US 7,312,237, provisional filed in 2001).

Lee et al. teach a combination which comprises (a) an anti-HER2 antibody or (b) at least one neoplastic agent including, but not limited to, microtubule affecting agents such as paclitaxel, anti-proliferative cytotoxic agents such as CPT-11, natural products such as doxorubicin, antiestrogens such as Tamoxifen, antiangiogenic compounds such as matloproteinase inhibitors, and steroids and (c) an epothilone derivative which appears to be identical to the claimed epothilone inhibitor referred to as epothilone B, wherein A is O, R is Me, z is O and R' is methyl (see attached structure obtained from STN (columns 11, lines 4-18 (Compound 1), and column 13, line 11 to column 14, line 38). The patent further teaches pharmaceutical compositions comprising the compounds described above with one or more pharmaceutically acceptable additional ingredients (column 20, lines 47-64). Lastly, the patent teaches that the combination may be administered simultaneously or sequentially (column 23, lines 47-50).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 21 and 29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lee et al. (US 7,312,237, provisional filed in 2001) as applied to claims 20, 22-28, 30-42, 44-45 and 50 above, in view of Herceptin® Package Insert (1998).

Lee et al. teach a combination which comprises (a) an anti-HER2 antibody or (b) at least one neoplastic agent including, but not limited to, microtubule affecting agents such as paclitaxel, anti-proliferative cytotoxic agents such as CPT-11, natural products such as doxorubicin, antiestrogens such as Tamoxifen, antiangiogenic compounds such as matloproteinase inhibitors, and steroids and (c) an epothilone derivative which appears to be identical to the claimed epothilone inhibitor referred to as epothilone B, wherein A is O, R is Me, z is O and R' is methyl (see attached structure

obtained from STN (columns 11, lines 4-18 (Compound 1), and column 13, line 11 to column 14, line 38). The patent further teaches pharmaceutical compositions comprising the compounds described above with one or more pharmaceutically acceptable additional ingredients (column 20, lines 47-64). Lastly, the patent teaches that the combination may be administered simultaneously or sequentially (column 23, lines 47-50).

Lee et al. do not explicitly teach that the anti-HER2 antibody is trastuzumab.

The Herceptin® Package insert teaches that Herceptin® is also referred to as trastuzumab and is a humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor2 protein, HER2 (see 1st paragraph of description). Moreover, the package insert teaches that trastuzumab is approved by the FDA for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein (see Indications and Usage).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to use in the combination taught by Lee et al. trastuzumab as the anti-HER2 antibody in view of the teachings of the Herceptin ® package insert. One would have been motivated to do so because the Herceptin® package insert teaches that trastuzumab is approved by the FDA for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Hence, one of ordinary skill in the art would have a reasonable expectation of success that by using trastuzumab in the combination taught by Lee et al. in view of the teachings of the Herceptin ® package insert, one would achieve a combination for the treatment of breast cancers which overexpress the HER-2 protein.

Claims 21, 26, 29-30, 36 and 42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514), as applied to claims 20, 22-23, 25, 27-28, 31-35, 37, 44-45 and 50 above, in view of Herceptin® Package Insert (1998).

Vite et al. teach a combination which comprises (a) a growth factor inhibitor such as a HER2 receptor monoclonal antibody or (b) a topoisomerase I or II inhibitor and (c) a epothilone derivative which appears to encompass the claimed epothilone derivaties of formula I (page 2, Compound V and page 10, lines 22-29). Moreover, the WO document teaches that the compounds

can be formulated with a pharmaceutical vehicle or diluent (page 11, lines 4-6). Lastly, the WO document teaches that epothilones A and B have been found to exert microtubule-stabilizing effects similar to paclitaxel and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease (page 1, lines 9-20).

Vite et al. do not explicitly teach that the anti-HER2 antibody is trastuzumab or that the epothilone derivative is epothilone B .

The Herceptin® Package insert teaches that Herceptin® is also referred to as trastuzumab and is a humanized monoclonal antibody that selectively binds with high affinity to the extracellular domain of the human epidermal growth factor receptor2 protein, HER2 (see 1st paragraph of description). Moreover, the package insert teaches that trastuzumab is approved by the FDA for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein (see Indications and Usage).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to use in the combination taught by Vite et al. trastuzumab as the anti-HER2 antibody in view of the teachings of the Herceptin ® package insert. One would have been motivated to do so because the Herceptin® package insert teaches that trastuzumab is approved by the FDA for the treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein. Moreover, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the epothilone derivatives as taught by Vite et al. for epothilone B in view of the teachings of Vite et al. One would have been motivated to do so because each of the agents have been taught in the prior art to be effective at inhibiting tumors cells. Hence, one of ordinary skill in the art would have a reasonable expectation of success that by using trastuzumab in the combination taught by Vite et al. in view of the teachings of the Herceptin ® package insert or substituting epothilone B for the epothilone derivatives taught by VIte et al., one would achieve a combination for the treatment of breast cancers which overexpress the HER-2 protein.

Claims 24 and 38-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vite et al. (WO 99/02514), as applied to claims 20, 22-23, 25, 27-28, 31-35, 37, 44-45 and 50 above, in view of Dixon et al. (Breast Cancer Research and Treatment 2001; 66: 191-199).

Vite et al. teach a combination which comprises (a) a growth factor inhibitor such as a HER2 receptor monoclonal antibody or (b) a topoisomerase I or II inhibitor and (c) a epothilone derivative which appears to encompass the claimed epothilone derivaties of formula I (page 2, Compound V and page 10, lines 22-29). Moreover, the WO document teaches that the compounds can be formulated with a pharmaceutical vehicle or diluent (page 11, lines 4-6). Lastly, the WO document teaches that epothilones A and B have been found to exert microtubule-stabilizing effects similar to paclitaxel and hence cytotoxic activity against rapidly proliferating cells, such as, tumor cells or other hyperproliferative cellular disease (page 1, lines 9-20).

Vite et al. do not explicitly teach that the combination includes an epothilone derivative and a aromatase inhibitor.

Dixon et al. teach that letrozole is a selective aromatase inhibitor which has been used successfully in the treatment of advanced breast cancer in menopausal women who had wither relapsed on adjuvant therapy or who had progressed while on anti-estrogen treatment for metastatic disease (page 192, 1st column, 1st full paragraph).

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of the references so as to include in the combination taught by Vite et al. letrozole in view of the teachings of Dixon et al. One would have been motivated to do so because each of the therapeutics had been individually taught in the prior art to be successful at treating cancer. Hence, The instant situation is amenable to the type of analysis set forth in In re Kerkhoven,205 USPQ 1069 (CCPA 1980) wherein the court held that it is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose in order to for a third composition that is to be used for the very same purpose since the idea of combining them flows logically from their having been individually taught in the prior art. Applying the same logic to the instant process claims, one of ordinary skill in the art would have reasonably expected to treat breast cancer since both had been demonstrated in the prior art to be effecitve.

Secondly, the strongest rationale for combining references is a recognition, expressly or impliedly in the prior art or drawn from a convincing line of reasoning based on established scientific principles or legal precedent, that some advantage or expected beneficial result would have

been produced by their combination. In re Sernaker, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983).

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20, 26-27, 32, 36-37, 42, 44-45 and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 18-21, 23 and 26 of copending Application No. 10/469,367 as evidenced by Hoffman et al. (Journal of Cellular Biochemistry; 2006; 98: 954-965). Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. For example, the combination which comprises (a) N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}4-(3-py- ridyl)-2-pyrimidine-amine and (b) an epothilone of formula I wherein A is O and R is a lower alkyl such as a methyl, and a pharmaceutical composition and commercial package comprising said combination claimed in the conflicting patent application appears to fall within the scope of the combination comprising (a) an anti-angiogenic agent and (b) an epothilone such as epothilone B as claimed in the application under examination because as evidenced by Hoffman et al. N-{5-[4-(4-methyl-piperazino-methyl)-benzoylamido]-2-methylphenyl}4-(3-py- ridyl)-2-pyrimidine-amine is an anti-angiogenic agent (page 961, 1st column, 5th line).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 20, 23, 26-27, 32, 34, 36-34, 42, 44-45, and 50 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 11-14 and 18-19 of copending Application No. 11/451,286 as evidenced by Hande (Biochimica et Biophysica Acta 1998; 1400: 173-184). Although the conflicting claims are not identical, they are not patentably distinct from each other because a species anticipates a genus. For example, the combination which comprises (a) an epothilone of formula I wherein A is O and R is a lower alkyl such as a methyl, and (b) at least one compounds selected from the group consisting of doxorubicin , a pharmaceutical composition and commercial package comprising said combination claimed in the conflicting patent application appears to fall within the scope of the combination comprising (a) topoisomerase II inhibitor and (b) an epothilone such as epothilone B as claimed in the application under examination because as evidenced by Hande doxorubicin is a topoisomerase II inhibitor (abstract).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Therefore, No claim is allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to BRANDON J. FETTEROLF whose telephone number is (571)272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Brandon J Fetterolf
Primary Examiner
Art Unit 1642

/Brandon J Fetterolf/
Primary Examiner, Art Unit 1642